RISK ASSESSMENT OF ANTIBIOTIC PREVALENCE IN DRINKING WATER AND ITS IMPACTS ON HUMAN HEALTH IN CHINA

LYU, J.[1,2,3] – YANG, L. S.[2,3] – CHEN, Y. Y.[1] – YE, B. X.[1] – ZHANG, L.[1*] – WANG, L.[2*]

[1]China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, No.29 Nanwei Road, Xicheng District, Beijing 100050, PR China
(e-mail: lvjia@nieh.chinacdc.cn; phone: +86-10-5093-0228; fax: +86-10-5093-0228)

[2]Key Laboratory of Land Surface Pattern and Simulation, Institute of Geographical Sciences and Natural Resources Research, Chinese Academy of Sciences, 11A, Datun Road, Chaoyang District, Beijing 100101, PR China
(e-mail: yangls@igsnrr.ac.cn; phone: +86-10-6488-9276; fax: +86-10-6485-4230)

[3]University of Chinese Academy of Sciences, 19(A) Yuquan Road, Shijingshan District, Beijing 100049, PR China

**Corresponding authors*
e-mail/phone/fax: zhanglan@nieh.chinacdc.cn/+86-10-5093-0224/+86-10-5093-0228; wangli@igsnrr.ac.cn/+86-10-6485-4841/+86-10-6485-4230

(Received 29th Jul 2020; accepted 19th Nov 2020)

Abstract. Drinking water is a known potential source of human exposure to antibiotics. However, risk of antibiotic exposure from drinking water has not been sufficiently quantified. We measured the levels of 23 antibiotics in drinking water from 12 cities of China during the summer and winter seasons, quantifying exposure doses and health risk quotients (HRQ) of antibiotic exposure via drinking water. High detection rates (above 70%) of macrolides (MLs), sulfonamides and fluoroquinolones were observed during summer season, with median concentrations of 0.26 ng/L, 0.59 ng/L and 0.36 ng/L, respectively, while only MLs were observed with a high detection rate in winter (median concentration 0.46 ng/L). Total antibiotic exposure via drinking water ranged from 0.0036 ng/kg/day to 4.36 ng/kg/day in summer and from 0.0046 ng/kg/day to 1.12 ng/kg/day in winter. High median antibiotic exposures were observed in Chaohu, Huainan and Guangzhou in summer and in Mudanjiang in winter. Of the 18 detected antibiotics, enrofloxacin, ciprofloxacin, sarafloxacin and roxithromycin had an HRQ $\geq$ 0.01. Drinking water is one of the principal pathways for human exposure to antibiotics. Accordingly, management of antibiotic exposure from drinking water should be a high public health priority, and the accompanying health risks merit greater attention from public health authorities.
Keywords: pollution, exposure, macrolides, sulfonamides, fluoroquinolones

Abbreviations: ADD: average daily potential dose, ADI: acceptable daily intake, DWTP: drinking water treatment plant, GP: glycopeptide, HLB: hydrophilic-lipophilic balance, HRQ: health risk quotient, LN: lincosamide, ML: macrolide, ND: not detected, QN: fluoroquinolone, RSC: relative source contribution, SA: sulfonamide, SPE: solid phase extraction, UPLC–MS/MS: ultra-performance liquid chromatography–tandem mass spectrometer, βL: β-lactam

Introduction

Antibiotics include a range of powerful medication ingredients that can destroy or slow the growth of bacteria and are extensively used to treat human and animal diseases and to promote animal growth (Le Page et al., 2017). The rising rate of antibiotic use has led to the contamination of potable water sources from natural bodies of water

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

receiving effluents from municipal wastewater treatment plants (hospital and community, Aga et al., 2016), agricultural sources (aquaculture, husbandry, Kümmerer, 2009), and the pharmaceutical industry (de Jesus Gaffney et al., 2015). Incomplete removal of antibiotics by conventional technologies (e.g., flocculation, sedimentation and disinfection) in drinking water treatment plants (DWTPs) leaves antibiotic residues in tap water, which now constitutes continuous human exposure to antibiotics (Yang et al., 2011). It is imperative to evaluate the exposure and health risks of antibiotics in drinking water.

In recent years, the issue of human health risk due to overuse of antibiotics has attracted substantial attention from the general public worldwide (Knapp et al., 2010). Antibiotics are understood to pose human health risks, including hypersensitive reactions, abnormalities in digestive functioning (Bedford, 2000), development and spread of antibiotic-resistant bacteria (Gullberg et al., 2011), and protracted toxic effects due to long-term low-level exposure (Sarmah et al., 2006). The occurrence of antibiotics in aquatic environments and drinking water is well-documented in developed countries including the USA (Benotti et al., 2009) and in the European Union (Carmona et al., 2014). China is one of the world's largest producers and consumers of antibiotics (Zhang et al., 2015). Previous investigations on antibiotic residues in aquatic environment have provided evidence that China has problems of antibiotic pollution (Ma et al., 2015; Xu, 2018). Thus, concerns are rising about antibiotic exposure from drinking water. However, studies measuring exposure to antibiotics in drinking water and associated health risks in China are limited.

The objectives of this study were to: (1) quantify the levels of 23 antibiotics in drinking water from 12 cities in different water basins in China, including seasonal and spatial distributions; (2) assess human exposure to antibiotics in drinking water in China; and (3) estimate the potential risks of antibiotic exposure via drinking water in the Chinese population.

Materials and methods

Water sampling and analysis

Tap water in China comes from the public water system and is treated at DWTPs for drinking and other household usages. Tap water samples were collected from 12 cities located in seven large river basins, three key lake basins and two key reservoir areas of China. Of the 12 cities sampled, 10 (Yibin, Lanzhou, Huainan, Shenyang, Mudanjiang, Guangzhou, Wuxi, Kunming, Chaohu and Chongqing) are prefecture-level cities with at least one million inhabitants and are located in the Yangtze River Basin, Yellow River Basin, Huaihe River Basin, Liaohe River Basin, Songhua River Basin, Pearl River Basin, Taihu Lake Basin, Dianchi Lake Basin, Chaohu Lake Basin, and Three Gorges Reservoir Area, respectively. Based on the population and number of DWTPs in each of these cities, five representative DWTPs were selected from each city for collection of tap water samples in corresponding water supply areas. The two remaining cities, Danjiangkou and Korla, are county-level cities with approximately one hundred thousand inhabitants and are located in the Danjiangkou Reservoir Area and Northwest River Basin, respectively. Based on the population and number of DWTPs in each of these cities, three DWTPs in Danjiangkou and one DWTP in Korla were selected for tap water sampling in corresponding water supply areas. This sampling plan yielded a total of 54 sampling points, from which tap water samples were collected in sunny or cloudy

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

weather in January and July 2017. The sampling locations are shown in *Figure 1*. Water samples were collected manually by qualified personnel in 2000 mL amber glass bottles with screw caps. The bottles were washed with water, methanol and ultrapure water and then dried prior to sample collection. A total of 30 mg of ascorbic acid was added for each liter of water as a pharmaceutical preservative (Lv et al., 2019). The water samples were maintained in dark conditions at 4 °C from the time of collection through reception and analysis at the laboratory.

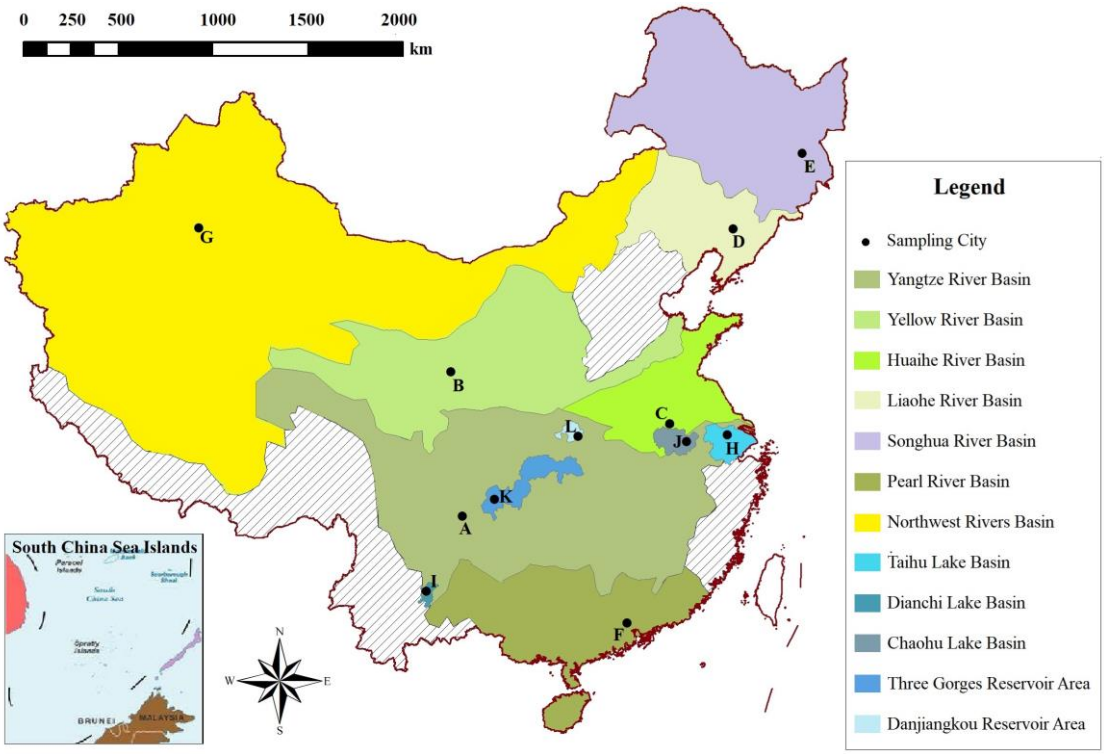

Figure 1. *Sampling locations, including cities and river basins. A, Yibin; B, Lanzhou; C, Huainan; D, Shenyang; E, Mudanjiang; F, Guangzhou; G, Korla; H, Wuxi; I, Kunming; J, Chaohu; K, Chongqing; L, Danjiangkou*

Twenty-three antibiotics of six different classes commonly used in China were analyzed, including four β-lactams (βLs), three macrolides (MLs), eight sulfonamides (SAs), six fluoroquinolones (QNs), one lincosamide (LN) and one glycopeptide (GP). Information on standards for analytes is listed in *Table A1* in the *Appendix*. Target analytes were extracted from water samples using solid phase extraction and then analyzed by ultra-performance liquid chromatography–tandem mass spectrometer. Field blanks and method blanks were created to identify any contaminant from the sampling site and analysis process. Recovery and precision were used to validate the method performance. Analysis process and its quality assurance were described in detail in the *Appendix*.

Exposure assessment via drinking water consumption

Drinking and dermal absorption are the main contaminant intake and uptake routes for human exposure to antibiotics through drinking water consumption. The average

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

daily potential dose (ADD) was used to evaluate antibiotic exposure through drinking and dermal absorption during water consumption, consumption of foods containing or cooked using water, and use of water for food washing and household activities including brushing teeth, bathing, and washing clothes.

ADD through intake water (ADD_{dw}) was calculated using *Equation 1:*

$$ADD_{dw} = \frac{C_{dw} \times IngR \times EF \times ED}{BW \times AT \times 1000} \quad \text{(Eq.1)}$$

where ADD_{dw} is the ADD from intake of water (μg/kg/day), C_{dw} is the concentration of antibiotics in drinking water (ng/L), IngR is the ingestion rate (L/day), including both direct and indirect ingestion, EF is the exposure frequency (days/year), ED is the exposure duration (years), BW is body weight (kg), and AT is averaging time (days). To reduce uncertainties in exposure variation between different geographical areas, across seasons, and between men and women, the IngR values corresponding to area, season and sex as well as the sex-specific BW value in China according to the *Exposure Factors Handbook of Chinese Population* (China EPA, 2009; area, season and sex-specific values are shown in *Table A2*) were used.

ADD through dermal absorption with water use (ADD_{dermal}) was calculated using *Equation 2:*

$$ADD_{dermal} = \sum_{i=1}^{9} \frac{DA_{event-i} \times SA_i \times EF_i \times ED_i}{BW \times AT_i} \quad \text{(Eq.2)}$$

where ADD_{dermal} is the ADD through dermal absorption (μg/kg/day). Dermal exposure was calculated from nine daily activities, including washing hands, face, hair, feet; washing vegetables, dishes, and clothes; bathing, and swimming. $DA_{event-i}$ refers to the absorbed dose from one event (μg/cm^2/day), as calculated using *Equation 3*. SA_i refers to the skin surface area available for contact (cm^2), according to the *Exposure Factors Handbook of Chinese Population* (China EPA, 2009; values summarized in *Table A3*). EF_i refers to the exposure frequency (days/year), ED_i to the exposure duration (years), BW to body weight (kg), and AT_i to averaging time (days). $DA_{event-i}$ was calculated as follows:

$$DA_{event-i} = K_p \times C \times T \times 10^{-6} \quad \text{(Eq.3)}$$

where K_p is the permeability coefficient (cm/hr), C is the chemical concentration in water that is in contact with the skin (ng/L), and T is the time of contact (hours/day), which was determined from references on water usage habits in northern and southern China (Duan et al., 2010; Huang et al., 2017), as summarized in *Table A4*.

It is difficult to obtain permeability coefficients of antibiotics directly from references. Accordingly, we used a model developed by ten Berge (2010) and recommended by Brown et al. (2016) in a study of eight models for calculating K_p by *Equation 4:*

$$\log K_p = -2.80 + 0.66 \log K_{ow} - 0.0056MW \quad \text{(Eq.4)}$$

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

where K_{ow} is the octanol/water partition coefficient of the target antibiotic and MW is the molecular weight (g/mole). K_{ow} and MW of target antibiotics are summarized in *Table A5*.

The total exposure to each antibiotic through drinking water consumption (ADD) was defined as the sum of ADD_{dw} and ADD_{dermal}. The ADD for the population of one area in a given season was calculated as the sex ratio-weighted average ADD. Sex ratios for each city were taken from the *China Statistical Yearbook* (National Bureau of Statistics, 2018; sex ratio values summarized in *Table A6*).

Health risk assessment

A health risk quotient (HRQ) is the ratio of a point estimate of exposure and a point estimate of health effects. HRQ for each antibiotic was calculated for each antibiotic by dividing its ADD by the acceptable daily intake (ADI) or risk-specific dose (RSD). HRQs were calculated using the most restrictive ADI or RSD for each antibiotic, which were adopted from provisional values established in the literature or derived using previously applied toxicological, microbiological or therapeutic approaches (Leung et al., 2013; Bengtsson-Palme and Larsson, 2016). The ADIs or RSDs used for HRQ calculation of each antibiotic are described in *Table A7*. The HRQ of each antibiotic in each city (HRQ_{ac}) was defined as the maximum HRQ of the antibiotic among all sampling points in the city. The total HRQ in each city (HRQ_{tc}) was the maximum value of the total HRQ for each sampling point (HRQ_{tp}), where HRQ_{tp} was the sum of HRQs for each antibiotic from each sampling point.

Results

Distribution of antibiotics in drinking water

Of 23 antibiotics quantified in this study, seventeen were detected in drinking water samples during the summer season, including three MLs, eight SAs, four QNs, one LN and one GP. Ten antibiotics were detected during the winter season, including one βL, two MLs, six SAs and one QN (*Fig. 2*). The detection rates and concentrations of antibiotics are summarized in *Table A8*. Detection rates in drinking water samples were above 70% during the summer for MLs, SAs and QNs, with median concentrations of 0.26 ng/L, 0.59 ng/L and 0.36 ng/L. During the winter, detection rates were above 70% only for MLs, with a median concentration of 0.46 ng/L.

The concentration levels of antibiotics in drinking water samples varied by city and season (*Fig. 3; Table A8*). In the summer, MLs were detected with a high median concentration of 10.12 ng/L in Guangzhou; the dominant ML was tylosin (range 6.82–15.04 ng/L). SAs and QNs were detected with high median concentrations of 2.73 ng/L and 3.41 ng/L respectively in Chaohu; the dominant antibiotics in these classes were sulfadiazine (0.81–5.20 ng/L), ciprofloxacin (1.17–1.94 ng/L), enrofloxacin (1.07–2.11 ng/L) and sarafloxacin (0.29–4.21 ng/L). SAs and QNs were also detected with high median concentrations of 1.73 ng/L and 6.40 ng/L, respectively, in Huainan; the dominant antibiotics in these classes were sulfamethoxazole (0.54–21.93 ng/L), sulfamethazine (0.11–7.63 ng/L), sulfadoxin (0.070–16.90 ng/L), ciprofloxacin (0.87–3.63 ng/L), enrofloxacin (1.97–4.47 ng/L) and sarafloxacin (0.82–1.64 ng/L). In the winter, SAs and MLs were detected with high median concentrations of 10.19 ng/L and 2.23 ng/L, respectively, in Mudanjiang; the dominant antibiotics in these classes were

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

sulfamethoxazole (1.27–6.82 ng/L), sulfadiazine (0.39–3.78 ng/L), trimethoprim (1.78–3.44 ng/L) and roxithromycin (0.39–17.28 ng/L). SAs were also detected in Lanzhou, Huainan and Chongqing with high median concentrations of 7.40 ng/L, 3.03 ng/L and 2.23 ng/L, respectively; the dominant SA in these cities was sulfamethoxazole (concentrations of 0.74–13.38 ng/L, 1.16–13.57 ng/L and 0.29–4.57 ng/L, respectively).

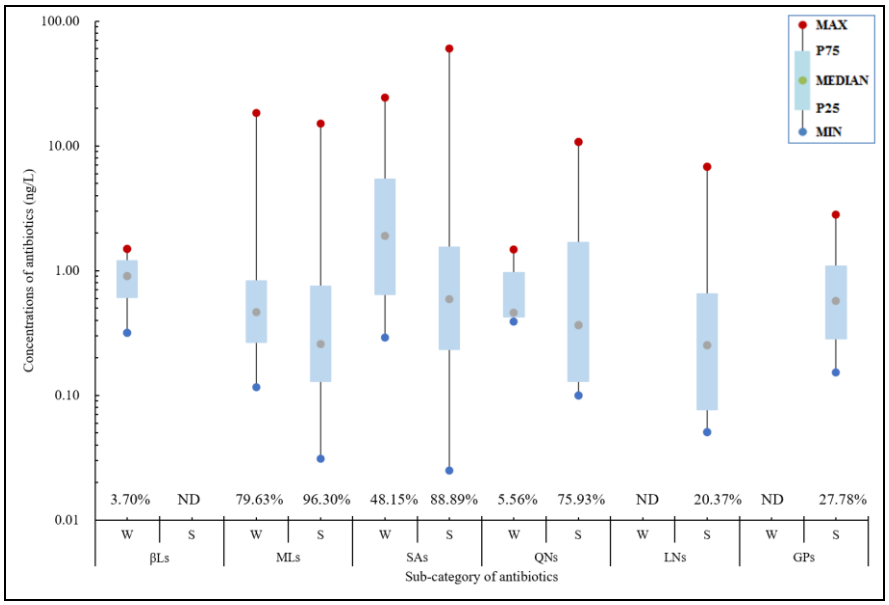

Figure 2. *Concentrations of antibiotics in drinking water samples in China. βLs, β-lactams; MLs, macrolides; SAs, sulfonamides; QNs, fluoroquinolones; LNs, lincosamides; GPs, glycopeptides; W, winter; S, summer; ND, not detected*

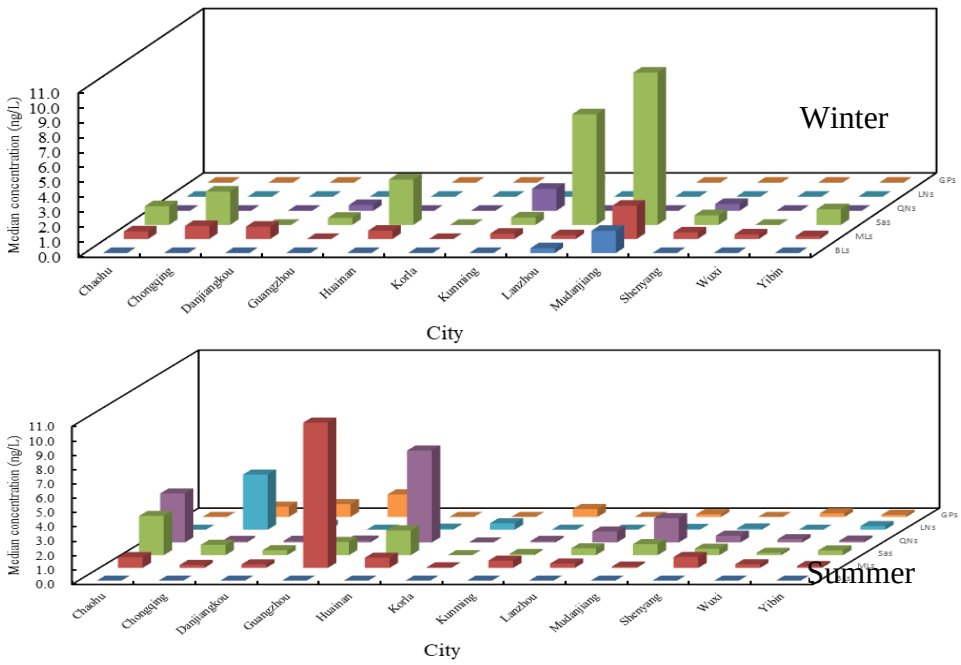

Figure 3. *Spatiotemporal distribution of six sub-categories of antibiotics in drinking water by city. βLs, β-lactams; MLs, macrolides; SAs, sulfonamides; QNs, fluoroquinolones; LNs, lincosamides; GPs, glycopeptides. Antibiotics were not detected in Korla in winter*

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Human exposure to antibiotics contaminated drinking water consumption

Exposure to antibiotics from drinking water varied across cities (*Fig. 4*). The median exposure dose to total antibiotics from drinking water was 0.071 ng/kg/day during summer season and 0.029 ng/kg/day during winter season. During summer, the highest median antibiotic exposure was observed in Chaohu (0.68 ng/kg/day), where exposure mainly derived from exposure to SAs (24.61–98.07%) and QNs (1.16–73.16%). Relatively high antibiotic exposure levels were also observed in Huainan, with a median dose of 0.62 ng/kg/day, also derived mainly from exposure to SAs (12.62–84.68%) and QNs (7.93–77.79%). Finally, relatively high exposure levels were observed in Guangzhou (median dose 0.48 ng/kg/day), where exposure was mainly derived from MLs (3.42–90.57%). The highest exposure in winter was observed in Huainan (median dose 4.36 ng/kg/day). During winter, the highest median exposure level was observed in Mudanjiang (0.47 ng/kg/day), mainly derived from SAs (39.56–79.83%) and MLs (16.00–60.44%).

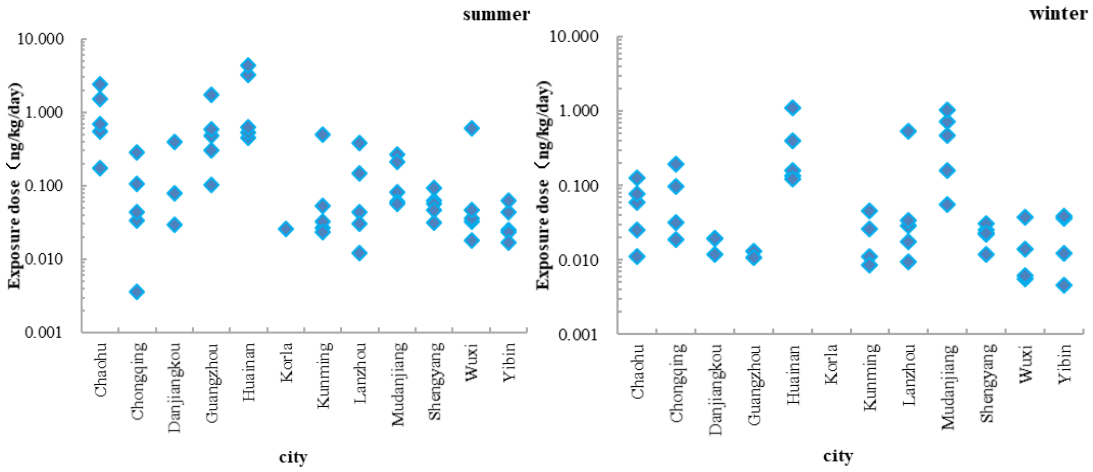

Figure 4. *Total antibiotic exposure via drinking water by city, sampling point and season*

Antibiotics were divided according to human or veterinary usage. Of 18 antibiotics detected in drinking water across summer and winter, 11 were used for both humans and animals, while 7 were used only for animals. Overall detection rates of veterinary antibiotics were 87.04% in the summer and 14.81% in the winter. Relatively high proportions of exposure to veterinary antibiotics were observed in Huainan, Guangzhou, Chaohu, Kunming and Mudanjiang during the summer, ranging from 22.71–58.44%, 44.73–97.64%, 16.14–57.41%, 40.51–97.30% and 30.91–69.31%, respectively (*Fig. 5*).

Risk assessment of antibiotics in drinking water

Among the eighteen antibiotics detected in at least one sample, HRQs for each antibiotic at each sampling point ranged from 1.8×10^{-8} to 0.13 in the summer and from 3.2×10^{-7} to 0.020 in winter. The maximum HRQ of each antibiotic in each city by season and the HRQ_{tc} are shown in *Figure 6*. Antibiotics with $HRQ \geq 0.01$ included three QNs (enrofloxacin, ciprofloxacin, sarafloxacin) and one ML (roxithromycin), with HRQ_{ac} ranging from 4.4×10^{-3} to 0.13, 4.6×10^{-3} to 0.11, 2.2×10^{-4} to 1.5×10^{-2} and 5.8×10^{-5} to 1.8×10^{-2}, respectively. Antibiotics with $HRQ \geq 0.0001$ and < 0.01

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

included one βL (cephalecxin), two MLs (clarithromycin and tylosin), three SAs (trimethoprim, sulfamethoxazole and sulfamethazine), lincomycin and virginiamycin, with HRQ_{ac} ranging from 9.3×10^{-5} to 3.9×10^{-4}, 5.1×10^{-4} to 4.8×10^{-3}, 2.1×10^{-3} to 4.5×10^{-3}, 2.8×10^{-4} to 9.4×10^{-3}, 1.2×10^{-5} to 2.7×10^{-3}, 5.5×10^{-6} to 2.9×10^{-4}, 3.3×10^{-5} to 3.5×10^{-3} and 9.5×10^{-5} to 1.7×10^{-3}, respectively. High HRQs were observed in Huainan, Kunming and Mudanjiang in both summer and winter, whereas Chaohu, Shenyang and Lanzhou had high HRQs only in summer. Enrofloxacin was the main risk component in Kunming in both winter and summer, and in Huainan, Chaohu, Mudanjaing in the summer. Ciprofloxacin was the main risk component in Huainan, Chaohu, Mudanjiang in summer. Roxithromycin was the main risk component in Mudanjiang in winter and in Lanzhou in summer, and sarafloxacin was the main risk component in Chaohu during the summer.

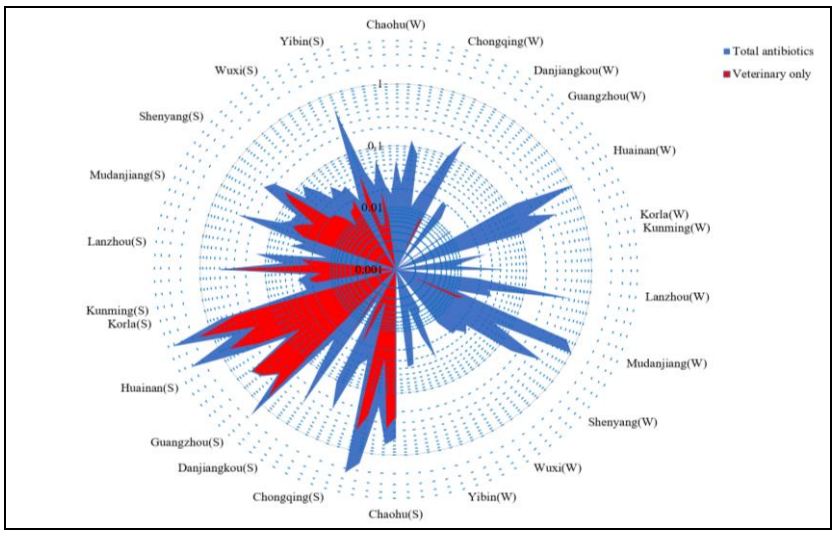

Figure 5. *Contribution of exposure to veterinary antibiotics to total antibiotic exposure through drinking water by city and season. W, winter; S, summer*

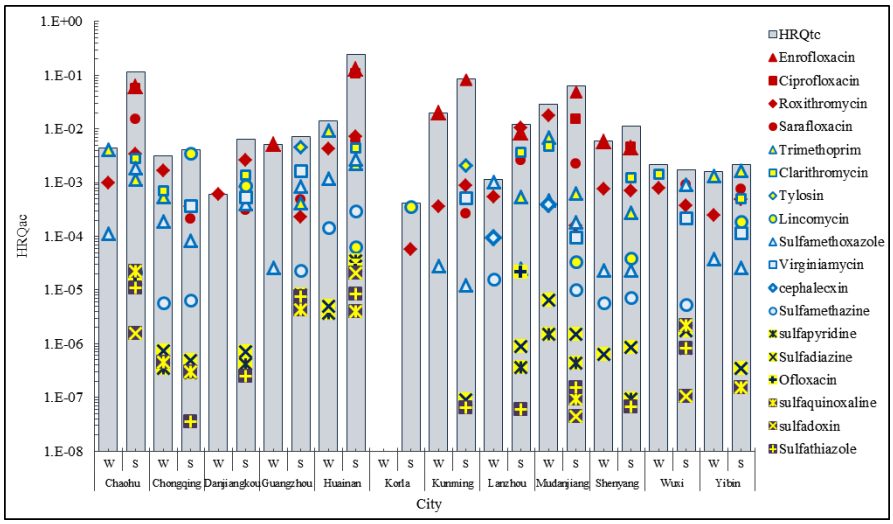

Figure 6. *HRQ_{ac} and HRQ_{tc} profiles of detected antibiotics in drinking water by city and season. HRQ_{ac}, maximum health risk quotient of the antibiotic among all sampling points in the city; HRQ_{tc}, total HRQ in each city; W, winter; S, summer*

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Discussion

In this study of antibiotic residues in drinking water from 12 cities in China, it was observed that large differences between regions and between summer and winter samples. Guangzhou, Chaohu and Huainan had the highest antibiotic levels in drinking water during the summer. Guangzhou is in the Pearl River Delta region located in South China and has among the highest antibiotic emission densities in China (Zhang et al., 2015). Chaohu and Huainan are in the Huaihe River watershed in eastern China and have the second highest antibiotic emission densities (Zhang et al., 2015). Exposure to antibiotics varied in summer and winter mainly because the dominant residues detected in drinking water. Among the dominant antibiotics detected during the summer months, tylosin, enrofloxacin and sarafloxacin are used only in veterinary medicine, indicating a significant contribution from increased usage of antibiotics in livestock, poultry breeding and aquaculture (Yang et al., 2011; He et al., 2016). The concentration of tylosin in drinking water in Guangzhou (6.82 ng/L to 15.04 ng/L) was higher than the residue level found in North Carolina, USA (4 ng/L, Ye et al., 2007). Although concentrations of SAs were relatively low in the summer compared to QNs and MLs, SAs did have high detection rates in both summer and winter, with high concentrations in Mudanjiang during winter. Sulfadiazine is widely used in veterinary medicine (Zheng et al., 2012). Sulfamethoxazole and sulfadiazine were grouped together, as sulfamethoxazole is used in veterinary medicine as well as in human medicine in China (Zhang et al., 2012).

The population of the 12 cities included in this study was generally exposed to antibiotics via water used for drinking and household purposes. Chaohu, Huainan and Guangzhou had summertime exposure doses that were more than five times the summertime exposures in other cities, whereas Mudanjiang had relatively high exposure doses in winter. Generally, human exposure to antibiotics comes from three sources: direct utilization, drinking water, and food (Wang et al., 2017). Urinary antibiotic levels were investigated in a general population study of adults aged 19 to 65 in Korea. Based on creatinine-adjusted urinary levels, the median daily intakes of sulfamethazine, trimethoprim, enrofloxacin and roxithromycin were estimated at 0.61 ng/kg/day, 0.054 ng/kg/day, 0.66 ng/kg/day, and 0.045 ng/kg/day, respectively, for men, and 0.73 ng/kg/day, 0.092 ng/kg/day, 0.71 ng/kg/day, 0.10 ng/kg/day, respectively, for women (Ji et al., 2010). The exposure contributions from drinking water to levels of these four antibiotics were 24%, 1.6%, 10%, and 46% for men and 11%, 1.5%, 9% and 26% for women. Sulfapyridine and sulfaquinoxaline, which are used only for animals, were not detected in meat, milk or aquatic products in Shanghai (Wang et al., 2017), indicating that the main exposure pathway for these two antibiotics is through drinking water, with particularly high exposures in winter. Some studies indicated that long-time boiling can break antibiotics residues in food (Tian et al., 2017). However, the effect of short-time boiling for antibiotic residues remove had not been well explored. In this study, drinking water boiling and indirect intake of water by food domestic cooking (such as rice and noodle) was not included. Additionally, this study evaluated the exposure in good weather in summer and winter, not considering the effect of rainny and snowy weather on water quality. Human exposure to antibiotics via medication use, food consumption and drinking water have not been well explored at the global level, and further investigation is required to improve understanding of the relative contribution of each of these pathways.

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

The HRQs of antibiotics varied across the different cities included in the study. Huainan, Chaohu, Kunming and Mudanjiang had relatively high HRQs in the summer, largely because the main antibiotic residues in these cities were enrofloxacin and ciprofloxacin, which had more restrictive ADIs for resistance selection pressure than other antibiotics. Among the four antibiotics with $HRQ \geq 0.01$, enrofloxacin and sarafloxacin are used only in veterinary medicine, whereas ciprofloxacin and roxithromycin are used in both human and veterinary medicine. The use of ciprofloxacin on animals in China is restricted, but in light of poor supervision, ciprofloxacin is still widely detected in water (including drinking water), soil, and food (Li et al., 2012; Xu et al., 2015; Wang et al., 2017). Based on the findings of our study, all the antibiotics detected posed a health risk less than 100%, though several posed significant risks. However, there are potential uncertainties in our analyses. Toxicities stemming from chronic exposure to trace amounts of antibiotic mixtures are not yet well understood (Rodriguez-Mozaz and Weinberg, 2010). Moreover, our assessment considered the relative source contribution (RSC) of ADIs from drinking water usage to be 100% based on a previous study (Leung et al., 2013). Based on a conservative estimate of RSC of 20%, the HRQs of antibiotics would increase five-fold, and these antibiotics would then pose potential health risks in Huainan during the summer ($HRQ_{ct} > 1$).

Conclusion

This study quantifies the seasonal and spatial distributions of 23 antibiotics in drinking water from 12 cities in different water basins in China. Exposure to antibiotics via drinking water and its potential risk are described. In light of the widespread detection of antibiotics in potable water, it appears that drinking water constitutes the main pathway for human exposure to antibiotics (especially veterinary antibiotics) in China. Among the antibiotics measured in our study, enrofloxacin, ciprofloxacin, roxithromycin and sarafloxacin were identified as posing the largest risk to human health. Moreover, there need further researches on adverse effects induced by exposure to antibiotics among sensitive groups such as children and pregnant women. The risk of antibiotic resistance by antibiotic exposure via drinking water also needs further studies for more precise evaluation.

Recommendations

Of 23 antibiotics measured, more than eight were detected in all 12 cities investigated, with the exception of Korla during the summer, indicating widespread population exposure to antibiotics via drinking water. Upgrading current treatment technologies of DWTPs is a possible mitigation measure (Li et al., 2018). Further test and evaluation of advanced treatments like ozonation, GAC filtration, nanofiltration and reverse osmosis need to be conducted (Yang et al., 2017). Controlling antibiotic inputs to water source is also highly recommended. Insufficient sewage treatment is a dominant factor explaining contamination of Chinese water sources (Li et al., 2014). Improved waste water treatment and control of the treatment process have to be employed for removal of these contaminants, and more research is needed to evaluate their behavior and fate in aquatic environment.

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Restriction of antibiotic usage at national level would like to be an effective measure to reduce the emission of antibiotics. In our study, enrofloxacin, ciprofloxacin, roxithromycin and sarafloxacin were identified as posing the largest risk to human health. Two of these antibiotics were used only in veterinary medicine, indicating a significant contribution from increased usage of antibiotics in livestock, poultry breeding and aquaculture. Restriction of veterinary antibiotic usage in agriculture and aquaculture would likely lead to reduced human exposure to antibiotics via drinking water, especially during the summer. Further study is needed to ascertain the causes of antibiotic usages and to make practical regulations for reducing the usage.

Improved supervision, surveillance and management plan should be implemented to limit the unnecessary use of antibiotics, especially in veterinary medicine. A comprehensive behavioral change communication strategy is central to the success of reduce risks of antibiotics exposure. Specific plans should be designed to restrict the use of antibiotic with high HRQ. Increased supervision is warranted to limit the usage of these antibiotics and to monitor their levels in drinking water.

Acknowledgements. This research is supported by the National Key R&D Program of China [2018YFC0407502, 2016YFD0801004]; the Science and Technology Project of Beautiful China Ecological Civilization Construction [XDA23100403]; and the Young Elite Scientist Sponsorship Program of Beijing Association for Science and Technology (2020-2022).

REFERENCES

[1] Aga, D. S., Lenczewski, M., Snow, D., Muurinen, J., Sallach, J. B., Wallace, J. S. (2016): Challenges in the measurement of antibiotics and in evaluating their impacts in agroecosystems: a critical review. – Journal of Environment Quality 45(2): 407-419. https://doi.org/10.2134/jeq2015.07.0393.

[2] Bedford, M. (2000): Removal of antibiotic growth promoters from poultry diets: implications and strategies to minimise subsequent problems. – World's Poultry Science Journal 56(4): 347-365.

[3] Bengtsson-Palme, J., Larsson, D. G. J. (2016): Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. – Environment International 86: 140-149. https://doi.org/10.1016/j.envint.2015.10.015.

[4] Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., Snyder, S. A. (2009): Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. – Environmental Science & Technology 43(3): 597-603. https://doi.org/10.1021/es801845a.

[5] Brown, T. N., Armitage, J. M., Egeghy, P., Kircanski, I., Arnot, J. A. (2016): Dermal permeation data and models for the prioritization and screening-level exposure assessment of organic chemicals. – Environment International 94: 424-435. https://doi.org/10.1016/j.envint.2016.05.025.

[6] Carmona, E., Andreu, V., Picó, Y. (2014): Occurrence of acidic pharmaceuticals and personal care products in Turia River Basin: from waste to drinking water. – Science of the Total Environment 484: 53-63. https://doi.org/10.1016/j.scitotenv.2014.02.085.

[7] China EPA. (2009): Exposure Factors Handbook of Chinese Population. – China Environmental Press, Beijing.

[8] de Jesus Gaffney, V., Almeida, C. M. M., Rodrigues, A., Ferreira, E., Benoliel, M. J., Cardoso, V. V. (2015): Occurrence of pharmaceuticals in a water supply system and

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

related human health risk assessment. – Water Research 72: 199-208. https://doi.org/10.1016/j.watres.2014.10.027.

[9] Duan, X. L., Zhang, W. J., Wang, Z. S., Guo, Y. M., Zhang, Y. S., Zhang, J. L. (2010): Water related activity and dermal exposure factors of people in typical areas of Northern China. – Research of Environmental Sciences 23(1): 55-61. https://doi.org/10.13198/j.res.2010.01.57.duanxl.009.

[10] Gullberg, E., Cao, S., Berg, O. G., Ilbäck, C., Sandegren, L., Hughes, D., Andersson, D. I. (2011): Selection of resistant bacteria at very low antibiotic concentrations. – PLoS Pathogens 7(7): e1002158. https://doi.org/10.1371/journal.ppat.1002158.

[11] He, X., Deng, M., Wang, Q., Yang, Y., Yang, Y., Nie, X. (2016): Residues and health risk assessment of quinolones and sulfonamides in cultured fish from Pearl River Delta, China. – Aquaculture (Amsterdam, Netherlands) 458: 38-46. https://doi.org/10.1016/j.aquaculture.2016.02.006.

[12] Huang, C., Ding, X., Zhang, L., Zhou, W. (2017): Analysis on drinking water exposure in Wuxi residents. – Journal of Environmental Hygiene 7(2): 95-101. https://doi.org/10.13421/j.cnki.hjwsxzz.2017.02.003.

[13] Ji, K., Kho, Y., Park, C., Paek, D., Ryu, P., Paek, D., Kim, M., Kim, P., Choi, K. (2010): Influence of water and food consumption on inadvertent antibiotics intake among general population. – Environmental Research 110(7): 641-649. https://doi.org/10.1016/j.envres.2010.06.008.

[14] Knapp, C. W., Dolfing, J., Ehlert, P. A. I., Graham, D. W. (2010): Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940. – Environmental Science & Technology 44(2): 580-587. https://doi.org/10.1021/es901221x.

[15] Kümmerer, K. (2009): Antibiotics in the aquatic environment—a review—part I. – Chemosphere 75(4): 417-434. https://doi.org/10.1016/j.chemosphere.2008.11.086.

[16] Le Page, G., Gunnarsson, L., Snape, J., Tyler, C. R. (2017): Integrating human and environmental health in antibiotic risk assessment: a critical analysis of protection goals, species sensitivity and antimicrobial resistance. – Environment International 109: 155-169. https://doi.org/10.1016/j.envint.2017.09.013.

[17] Leung, H. W., Jin, L., Wei, S., Tsui, M. M. P., Zhou, B., Jiao, L., Cheung, P. C., Chun, Y. K., Murphy, M. B., Lam, P. K. S. (2013): Pharmaceuticals in tap water: human health risk assessment and proposed monitoring framework in China. – Environmental Health Perspectives 121(7): 839-846. https://doi.org/10.1289/ehp.1206244.

[18] Li, W., Shi, Y., Gao, L., Liu, J., Cai, Y. (2012): Occurrence of antibiotics in water, sediments, aquatic plants, and animals from Baiyangdian Lake in North China. – Chemosphere 89(11): 1307-1315. https://doi.org/10.1016/j.chemosphere.2012.05.079.

[19] Li, X., Shi, H., Li, K., Zhang, L., Gan, Y. (2014): Occurrence and fate of antibiotics in advanced wastewater treatment facilities and receiving rivers in Beijing, China. – Frontiers of Environmental Science & Engineering 8(6): 888-894. https://doi.org/10.1007/s11783-014-0735-0.

[20] Li, G., Yang, H., An, T., Lu, Y. (2018): Antibiotics elimination and risk reduction at two drinking water treatment plants by using different conventional treatment techniques. – Ecotoxicology and Environmental Safety 158: 154-161. https://doi.org/10.1016/j.ecoenv. 2018.04.019.

[21] Lv, J., Zhang, L., Chen, Y., Ye, B., Han, J., Jin, N. (2019): Occurrence and distribution of pharmaceuticals in raw, finished, and drinking water from seven large river basins in China. – Journal of Water and Health 17(3): 477-489. https://dx.doi.org/10.2166/wh. 2019.250.

[22] Ma, Y., Li, M., Wu, M., Li, Z., Liu, X. (2015): Occurrences and regional distributions of 20 antibiotics in water bodies during groundwater recharge. – Science of the Total Environment 518-519: 498-506. https://doi.org/10.1016/j.scitotenv.2015.02.100.

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

[23] Rodriguez-Mozaz, S., Weinberg, H. S. (2010): Meeting report: pharmaceuticals in water—an interdisciplinary approach to a public health challenge. – Environmental Health Perspectives 118(7): 1016-1020. https://doi.org/10.1289/ehp.0901532.
[24] Sarmah, A. K., Meyer, M. T., Boxall, A. B. A. (2006): A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. – Chemosphere 65(5): 725-759. https://doi.org/10.1016/j.chemosphere.2006.03.026.
[25] ten Berge, W. (2010): QSARs for skin permeation of chemicals. – https://home.wxs.nl/~wtberge/qsarperm.html.
[26] Tian, L., Khalil, S., Bayen, S. (2017): Effect of thermal treatments on the degradation of antibiotic residues in food. – Critical Reviews in Food Science and Nutrition 57(17): 3760. https://doi.org/10.1080/10408398.2016.1164119.
[27] Wang, H., Ren, L., Yu, X., Hu, J., Chen, Y., He, G., Jiang, Q. (2017): Antibiotic residues in meat, milk and aquatic products in Shanghai and human exposure assessment. – Food Control 80: 217-225. https://doi.org/10.1016/j.foodcont.2017.04.034.
[28] Xu, Y., Chen, T., Wang, Y., Tao, H., Liu, S., Shi, W. (2015): The occurrence and removal of selected fluoroquinolones in urban drinking water treatment plants. – Environmental Monitoring and Assessment 187(12): 729. https://doi.org/10.1007/s10661-015-4963-y.
[29] Xu, Z., Li, T., Bi, J., Wang, C. (2018): Spatiotemporal heterogeneity of antibiotic pollution and ecological risk assessment in Taihu Lake Basin, China. – Science of the Total Environment 643: 12-20. https://doi.org/10.1016/j.scitotenv.2018.06.175.
[30] Yang, J. F., Ying, G. G., Zhao, J. L., Tao, R., Su, H. C., Liu, Y. S. (2011): Spatial and seasonal distribution of selected antibiotics in surface waters of the Pearl Rivers, China. – Journal of Environmental Science and Health, Part B 46(3): 272-280. https://doi.org/10.1080/03601234.2011.540540.
[31] Yang, Y., Sik Ok, Y., Kim, K. H., Kwon, E. E., Tsang, Y. F. (2017): Occurrences and removal of pharmaceuticals and personal care products (PPCPs) in drinking water and water/sewage treatment plants: a review. – Science of the Total Environment 596-597: 303-320. http://dx.doi.org/10.1016/j.scitotenv.2017.04.102.
[32] Ye, Z., Weinberg, H. S., Meyer, M. T. (2007): Trace analysis of trimethoprim and sulfonamide, macrolide, quinolone, and tetracycline antibiotics in chlorinated drinking water using liquid chromatography electrospray tandem mass spectrometry. – Analytical Chemistry 79(3): 1135-1144. https://doi.org/10.1021/ac060972a.
[33] Zhang, R., Zhang, G., Tang, J., Xu, W., Li, J., Liu, X., Zou, Y., Chen, X., Li, X. (2012): Levels, spatial distribution and sources of selected antibiotics in the East River (Dongjiang), South China. – Aquatic Ecosystem Health & Management 15(2): 210-218. https://doi.org/10.1080/14634988.2012.689576.
[34] Zhang, Q. Q., Ying, G. G., Pan, C. G., Liu, Y. S., Zhao, J. L. (2015): Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. – Environmental Science & Technology 49(11): 6772-6782. https://doi.org/10.1021/acs.est.5b00729.
[35] Zheng, Q., Zhang, R., Wang, Y., Pan, X., Tang, J., Zhang, G. (2012): Occurrence and distribution of antibiotics in the Beibu Gulf, China: impacts of river discharge and aquaculture activities. – Marine Environmental Research 78: 26-33. https://doi.org/10.1016/j.marenvres.2012.03.007.

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

APPENDIX

Risk assessment of prevalence of antibiotics in drinking water and impacts on human health exposed to antibiotic contamination – China

Analysis method (Lv et al., 2019)

Sample extraction

Target analytes were extracted from the water samples using SPE. One liter water samples were acidified to pH 2.0–2.5 with phosphoric acid and potassium phosphate monobasic. The samples were spiked with isotopically labeled standards, at a concentration of 20 ng, and 500 mg EDTA-2Na were added. Detailed information on internal standards is shown in *Table A1*.

The water samples were loaded on the automated SPE system at an approximate rate of 5 mL/min (Visiprep-DL 24-Ports SPE Vacuum Manifold, Supelco, USA). Oasis hydrophilic-lipophilic balance (HLB) cartridges (6 mL, 200 mg of sorbent, Waters, USA) were used for sample pretreatment. The cartridges were conditioned with 10 mL methanol and 10 mL ultrapure water prior to sample loading. After sample loading, the cartridges were rinsed with 10 mL ultrapure water, dried for 10 min under vacuum and eluted with 10 mL methanol. The eluates were concentrated to near dryness under a gentle stream of nitrogen in a 30 °C water bath and reconstituted in 1 mL of water/methanol (95/5; v/v). The concentrated extracts were then analyzed by UPLC–MS/MS.

UPLC-MS/MS analysis

A UPLC system (ACQUITY UPLC, Waters, USA) equipped with a Waters ACQUITY UPLC HSS T3 column (100 mm × 2.1 mm and 1.8 μm particle size) was used to separate the analytes. The column temperature was 40 °C, the injection volume was 10 μL, and the flow rate was 0.35 mL/min. The mobile phases consisted of water with 0.1% (v/v) formic acid (A) and methanol (B), and the following elution program was employed: 95% (A) to 80% (A) from 0 to 3 min, 80% to 70% (A) from 3 to 6 min, 70% to 60% (A) from 6 to 10 min, 60% to 30% (A) from 10 to 12 min, 30% to 5% (A) from 12 to 15 min, and then 95% (A) from 15 to 15.5 min. Finally, the column was re-equilibrated for 2.5 min before the next injection, for a total run time of 18 min.

A Waters TQ-S micro triple quadrupole mass spectrometer (Waters Technologies, USA) equipped with an electrospray ion source was used for the analysis of the pharmaceuticals. Multiple reaction monitoring (MRM) mode was used for quantitative analysis, and all pharmaceuticals were measured in positive ion mode. The source temperature was 120 °C, the desolvation temperature was 350 °C, the desolvation gas flow was 650 L/h, the collision gas flow was 50 L/h, and the capillary voltage was 2.0 kV.

Method performance and quality assurance

The determination of linearity, LOD and LOQ, recovery and precision were used to validate the method. Calibration curves were generated using mixtures of standards at concentrations from 0.05 to 100 μg/L and isotopically-labeled internal standards at a

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

concentration of 20 μg/L. Good linearity was observed, with correlation coefficients greater than 0.99.

The analytes were identified by their retention times, two characteristic ion transitions and specific ion ratios (deviation < 20% with respect to analytical standard ratios). Spiked ultrapure water with various concentrations were extracted and analyzed to determine the LOD and LOQ. The LOD and LOQ were defined as the lowest concentrations that gave signal-to-noise ratios greater than 3 and 10, respectively.

Field blanks and method blanks were created to identify any contaminant from the sampling site and analysis process. Recovery and precision were used to validate the method performance. Percent recovery and precision were determined using ultrapure water and spiked matrix samples (raw water and finished water) at three concentrations (5, 10, and 40 ng/L) and the IS solution (20 ng/L). Six replicates of each concentration were used to evaluate the analyte recovery during sample pretreatment and UPLC-MS/MS analysis. The recoveries as expressed as the average of six replicates. The recoveries and precision varied with the natures of the analytes, and an acceptable result was generated (U.S. EPA, 2007).

Table A1. *Detailed information about target analytes standards and internal standards. βLs, β-lactams; MLs, macrolides; SAs, sulfonamides; QNs, fluoroquinolones; LN, lincosamide; GP, glycopeptide. IS, Internal standard*

Antibiotics	CAS No.	Class of antibiotics	Molecular formula	Molecular weight
Penicillin G	61-33-6	βLs	$C_{16}H_{17}N_2O_4S$	334.39
Cloxacillin	61-72-3	βLs	$C_{19}H_{18}ClN_3O_5S$	435.88
Cephalecxin	23325-78-2	βLs	$C_{16}H_{17}N_3O_4S$	365.4
Ceftiofur	80370-57-6	βLs	$C_{19}H_{17}N_5O_7S_3$	523.56
Clarithromycin	81103-11-9	MLs	$C_{38}H_{69}NO_{13}$	747.95
Roxithromycin	80214-83-1	MLs	$C_{41}H_{76}N_2O_{15}$	837.05
Tylosin	1401-69-0	MLs	$C_{46}H_{77}NO_{17}$	916.1
Sulfapyridine	144-83-2	SAs	$C_{11}H_{11}N_3O_2S$	249.29
Sulfadiazine	68-35-9	SAs	$C_{10}H_{10}N_4O_2S$	250.28
Sulfamethoxazole	723-46-6	SAs	$C_{10}H_{11}N_3O_3S$	253.28
Sulfathiazole	72-14-0	SAs	$C_9H_9N_3O_2S_2$	255.32
Sulfamethazine	57-68-1	SAs	$C_{12}H_{14}N_4O_2S$	278.33
Sulfaquinoxaline	59-40-5	SAs	$C_{14}H_{12}N_4O_2S$	300.34
Sulfadoxin	2447-57-6	SAs	$C_{12}H_{14}N_4O_4S$	310.33
Trimethoprim	738-70-5	SAs	$C_{14}H_{18}N_4O_3$	290.32
Norfloxacin	70458-96-7	QNs	$C_{16}H_{18}FN_3O_3$	319.33
Ciprofloxacin	85721-33-1	QNs	$C_{17}H_{18}FN_3O_3$	331.34
Enrofloxacin	93106-60-6	QNs	$C_{19}H_{22}FN_3O_3$	359.39
Ofloxacin	82419-36-1	QNs	$C_{18}H_{20}FN_3O_4$	361.37
Clinafloxacin	105956-97-6	QNs	$C_{17}H_{17}ClFN_3O_3$	365.79
Sarafloxacin	98105-99-8	QNs	$C_{20}H_{17}F_2N_3O_3$	385.36
Lincomycin	154-21-2	LN	$C_{18}H_{34}N_2O_6S$	406.54
Virginiamycin	11006-76-1	GP	$C_{28}H_{35}N_3O_7$	525.59
D_8-Ciprofloxacin	——	IS	$C_{17}H_{10}D_8FN_3O_3$	339.39
$^{13}C_6$ Sulfamethazine	——	IS	$C_6{}^{13}C_6H_{14}N_4O_2S$	284.29
$^{13}C_3$-Trimethoprim	——	IS	$C_{11}{}^{13}C_3H_{18}N_4O_3$	293.3
^{13}C-D_3-Erythromycin	——	IS	$C_{36}{}^{13}CH_{64}D_3NO_{13}$	737.94
D_3-Lincomycin	——	IS	$C_{18}H_{31}D_3N_2O_6S$	409.56
D_5-cephalexcin	——	IS	$C_{16}H_{14}D_5N_3O_4S$	370.43
$^{13}C_6$-Sulfamethoxazole	——	IS	$C_4{}^{13}C_6H_{11}N_3O_3S$	259.21
D_8-Sarafloxacin	——	IS	$C_{20}H_9D_8F_2N_3O_3$	393.4

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Table A2. *IngR values corresponding to area, season and sex in China*

Area	Season	Gender	IngR (L/day)
Liaoning	winter	male	1742
Heilongjiang	winter	male	1881
Jiangsu	winter	male	2267
Anhui	winter	male	2944
Hubei	Winter	Male	1500
Guangdong	Winter	Male	1695
Chongqing	Winter	Male	1215
Sichuan	Winter	Male	1862
Yunnan	Winter	Male	1895
Gansu	Winter	Male	2587
Xinjiang	Winter	Male	2974
Liaoning	Summer	Male	2090
Heilongjiang	Summer	Male	2196
Jiangsu	Summer	Male	3204
Anhui	Summer	Male	4063
Hubei	Summer	Male	2570
Guangdong	Summer	Male	2411
Chongqing	Summer	Male	2053
Sichuan	Summer	Male	3184
Yunnan	Summer	Male	2719
Gansu	Summer	Male	3990
Xinjiang	Summer	Male	3716
Liaoning	Winter	Female	1425
Heilongjiang	Winter	Female	2180
Jiangsu	Winter	Female	1817
Anhui	Winter	Female	2432
Hubei	Winter	Female	1366
Guangdong	Winter	Female	1663
Chongqing	Winter	Female	1293
Sichuan	Winter	Female	1691
Yunnan	Winter	Female	1492
Gansu	Winter	Female	2050
Xinjiang	Winter	Female	2086
Liaoning	Summer	Female	1706
Heilongjiang	Summer	Female	1826
Jiangsu	Summer	Female	2558
Anhui	Summer	Female	3423
Hubei	Summer	Female	2376
Guangdong	Summer	Female	2347
Chongqing	Summer	Female	2164
Sichuan	Summer	Female	3062
Yunnan	Summer	Female	2203
Gansu	Summer	Female	3133
Xinjiang	Summer	Female	2703

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Table A3. *The skin surface area available for contact (cm^2)*

SA_i (cm^2)	Hand cleaning	Face and hair cleaning	Foot cleaning	Dish washing	Vegetable washing	Clothes washing	Bathing	Swimming
Male	800	1300	1100	800	800	800	17000	6300
Female	700	1200	1000	700	700	700	15000	5700

Table A4. *The time of contact (T, hours/day) on water usage habits in northern and southern China*

Time of contact (hours/day)	Hand cleaning	Face and hair cleaning	Foot cleaning	Dishes washing	Vegetable washing	Clothes washing	Bathing	Swimming
Male in South China	0.0500	0.0783	0.0167	0.0000	0.0000	0.0000	0.1750	0.086
Female in South China	0.0667	0.1117	0.0117	0.0850	0.0717	0.0467	0.2083	0.088
Male in North China	0.0627	0.1012	0.0146	0.0115	0.0091	0.0462	0.2553	0.086
Female in North China	0.0614	0.1168	0.0165	0.1606	0.1364	0.3050	0.2424	0.088

Table A5. *Kow and MW of target antibiotics*

Antibiotic	log Kow	MW (g/mol)
Penicillin G	1.83	334.38
Cloxacillin	2.44	435.88
Cephalecxin	0.65	347.39
Ceftiofur	1.6	523.57
Clarithromycin	3.16	747.95
Roxithromycin	2.21	837.05
Tylosin	1.63	916.11
Sulfapyridine	0.35	249.29
Sulfadiazine	2.59	250.27
Sulfamethoxazole	0.89	253.28
Sulfathiazole	0.05	255.32
Sulfamethazine	0.14	278.33
Sulfaquinoxaline	1.68	300.34
Sulfadoxin	0.43	310.33
Norfloxacin	0.46	319.33
Ciprofloxacin	0.28	331.34
Enrofloxacin	0.64	359.4
Ofloxacin	-0.39	371.37
Sarafloxacin	0.57	385.36
Lincomycin	0.2	406.54
Trimethoprim	0.91	290.32

Table A6. *Sex ratios for each city*

City	Gender ratio (population of male/population of female)
Chaohu	0.5162
Chongqing	0.5127
Danjiangkou	0.5158
Guangzhou	0.5016
Huainan	0.525
Kuerle	0.5109
Kunming	0.5141
Lanzhou	0.5037
Mudanjiang	0.501
Shenyang	0.4941
Wuxi	0.5033
Yibin	0.5197

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236

Table A7. *The acceptable daily intake (ADI) or risk-specific dose (RSD) used for HRQ calculation of each antibiotic*

Antibotic	ADI or RSD (ug/kg/day)	Toxicity or effect endpoint
Cephalecxin	0.13	Resistance selection
Clarithromycin	0.0083	Resistance selection
Roxithromycin	0.033	Resistance selection
Tylosin	0.13	Resistance selection
Sulfapyridine	10	Microbiological
Sulfadiazine	20	Reduced fetal bodyweight and C-R length at the next higher dose
Sulfamethoxazole	0.5	Resistance selection
Sulfathiazole	50	Changes in thyroid tissue. a NOEL of 5 mg/kg for the thyroid effects in animal studies
Sulfamethazine	1.6	Thyroid gland follicular adenoma in rats with tumor incidence data
Sulfaquinoxaline	10	Increased thyroid weights at the next higher dose
Sulfadoxin	50	Increased liver weights at the next higher dose
Norfloxacin	0.017	Resistance selection
Ciprofloxacin	0.0021	Resistance selection
Enrofloxacin	0.0021	Resistance selection
Ofloxacin	3.2	Microbiological
Sarafloxacin	0.017	Resistance selection
Lincomycin	0.067	Resistance selection
Virginiamycin	0.067	Resistance selection
Trimethoprim	0.017	Resistance selection

Table A8. *The significance level of the antibiotic concentrations across cities and seasons*

Class of antibiotics	Nonparametric tests	Significance level	
		Across seasons	Across cities
β-lactams	Mann Whitney U test	0.206	——
	Kolmogorov-Smirnov test	0.001*	——
	Wald Wolfwitz Runs	——	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.0001*
Macrolides	Mann Whitney U test	0.065	——
	Kolmogorov-Smirnov test	0.007*	——
	Wald Wolfwitz Runs	0.002*	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.0001*
Sulfonamides	Mann Whitney U test	0.0001*	——
	Kolmogorov-Smirnov test	0.0001*	——
	Wald Wolfwitz Runs	0.0001*	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.0001*
Fuoroquinolones	Mann Whitney U test	0.0001*	——
	Kolmogorov-Smirnov test	0.0001*	——
	Wald Wolfwitz Runs	0.0001*	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.015*
Lincosamide	Mann Whitney U test	0.0001*	——
	Kolmogorov-Smirnov test	0.187	——
	Wald Wolfwitz Runs	0.0001*	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.0001*
Glycopeptide	Mann Whitney U test	0.0001*	——
	Kolmogorov-Smirnov test	0.034*	——
	Wald Wolfwitz Runs	0.0001*	——
	Median test	——	0.0001*
	Kruskal-Wallis test	——	0.0001*

Mann Whitney U test, Kolmogorov-Smirnov test and Wald Wolfwitz Runs were conducted for the seasonal differences between winter and summer; Median test and Kruskal-Wallis test were conducted for the spatial differences across 12 cities. *The significance level is 0.05

http://www.aloki.hu ● ISSN 1589 1623 (Print) ● ISSN 1785 0037 (Online)
DOI: http://dx.doi.org/10.15666/aeer/1901_219236